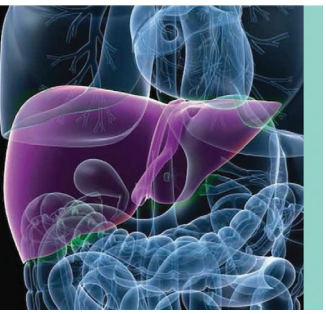

Hepatitis E: Current Status in India

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Hepatitis E, caused by infection with hepatitis E virus (HEV), is the commonest cause of acute viral hepatitis among adults in India. Human HEV, a member of family Hepeviridae and genus *Orthohepevirus A*, has four main genotypes (GT1-GT4). Of these, GT1 and GT2 infect only humans, whereas GT3 and GT4 circulate naturally in several mammalian animals, such as pigs, with occasional zoonotic transmission to humans.[1] The various genotypes have distinct geographical distributions (Fig. 1) and are associated with specific routes of transmission and clinical spectrum of disease.[2]

In India, hepatitis E, whether occurring in epidemic form[3] or as sporadic cases,[4] is caused exclusively by GT1 HEV. Hence clinical and epidemiological characteristics of hepatitis E in India differ from those of HEV-related disease in developed countries of Europe and North America, where GT3 virus is more prevalent, and the Far East, where GT4 virus is more prevalent.

EPIDEMIOLOGY

HEV infection and disease are highly endemic in India, with nearly 60% of blood donors having circulating anti-HEV IgG antibodies, indicating prior exposure to the virus. The seroprevalence rates vary by age, being higher in the elderly.[5] Overall, hepatitis E accounts for nearly 50% of acute hepatitis cases and for a similar proportion of acute liver failure (ALF) cases.

In India, the transmission of HEV is mostly human to human and through the fecal-oral route. The virus is excreted in the feces of infected persons for a few days before and up to around 3 weeks after the onset of illness[6]; it is transmitted to susceptible hosts through contamination of drinking water supplies or food. The infection can occur as outbreaks or as sporadic cases. Outbreaks often occur during the rainy season or follow periods of flooding, when the opportunities for contamination of drinking water with sewage increase. The risk for person-to-person transmission is quite small, as is evident from low secondary attack rates among family members and other close contacts of those affected.

Zoonotic transmission, which is believed to be the commonest route in developed countries, appears to be nonexistent or rare in India. This is supported by the fact that although a very large proportion of pigs in India have

Abbreviations: ALF, acute liver failure; HEV, hepatitis E virus.

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demonstrable anti-HEV antibodies, the virus isolates from them have belonged to GT4, being very different from those in human cases.[7]

The epidemiology of hepatitis E in India has not changed much over time. The outbreaks occur periodically, although all of them do not necessarily make it to the published literature. During the years 2011 to 2013, 291 outbreaks of hepatitis were reported to the country's Integrated Disease Surveillance Programme; of the 163 outbreaks with a known cause, 78 were related to hepatitis E.[8]

CLINICAL SPECTRUM OF GENOTYPE 1 DISEASE

Manifestations of HEV infection are quite diverse and include asymptomatic infection, nonspecific viral syndrome, elevation of liver enzymes without any jaundice (anicteric hepatitis), icteric hepatitis, and ALF. Overall, asymptomatic infection and anicteric hepatitis appear to be more common than icteric hepatitis; the latter is more frequent in adults than in children. Most of those affected have complete resolution with no residual liver damage, except for some persons with ALF who succumb.

The clinical patterns of GT1 infection in India are different from those seen in low-endemic, developed countries in Europe and North America with GT3 dominance (Table 1).[2] The main differences relate to the following: (1) a particular propensity for severe disease in pregnant women, (2) lack of persistent HEV infection and chronic hepatitis E, and (3) lack of transfusion-related hepatitis E. In addition, extrahepatic manifestations of HEV infection other than pancreatitis, such as neurological manifestations, have been infrequent in the Indian population despite a high incidence of hepatic disease.

HEV in Pregnancy

In areas with predominance of GT1 HEV, pregnant women develop a more severe disease. Thus, during outbreaks in these areas, women in the second or third trimester of gestation are at a greater risk for development of symptomatic disease than are nonpregnant women and men (Fig. 2).[9] Further, HEV-infected pregnant women carry a greater risk for progression to ALF, as compared with nonpregnant persons with hepatitis E. HEV infection in pregnancy is also associated with an increased risk for adverse obstetric, maternal, and fetal outcomes, such as intrauterine death, premature delivery, postpartum hemorrhage, and neonatal deaths. Such an association between HEV infection and pregnancy has not been reported from areas with predominant circulation of GT3/GT4 HEV. The exact mechanism underlying this association remains unclear; however, viral, hormonal,

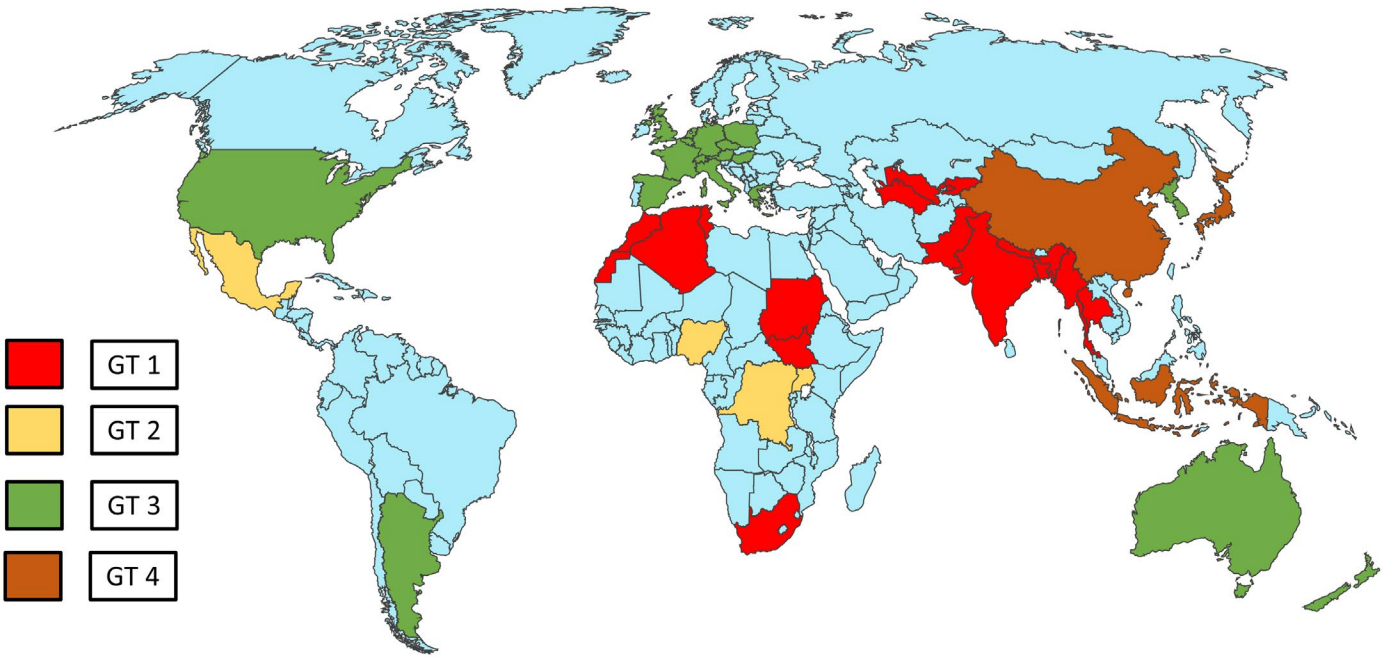

FIG 1 Predominant HEV genotypes in different parts of the world.

TABLE 1. COMPARISON OF FEATURES OF HEV INFECTION IN INDIA VERSUS THAT IN DEVELOPED COUNTRIES

Feature	India	Developed Countries
Endemicity	High to very high	Low
Predominant virus genotype	1	Mostly 3 or 4
Predominant route of transmission	Fecal-oral	Zoonotic
Animal reservoirs	None identified	Pigs (most common), wild boars, deer
Characteristics of affected persons	Young adults, mostly those in good health	Elderly; mostly those with preexisting disease, e.g., immunocompromised states, organ transplant recipients
Spectrum of illness	Asymptomatic, acute viral hepatitis, ALF	Asymptomatic, acute hepatitis, chronic hepatitis that may progress to cirrhosis
Severity of acute hepatitis	Variable: asymptomatic, mild or severe, including ALF	Mostly mild to moderate; severe disease (ALF) is rare
Nonhepatic manifestations	Uncommon; can manifest as acute pancreatitis	Common; associated with hematological and neurological illnesses
Association with pregnancy	A greater risk for severe disease and fatal outcome among pregnant women	Appears to have no particular association, although information is relatively limited
Chronic infection	None to occasional	Frequent
Treatment	None	Ribavirin or pegylated interferon

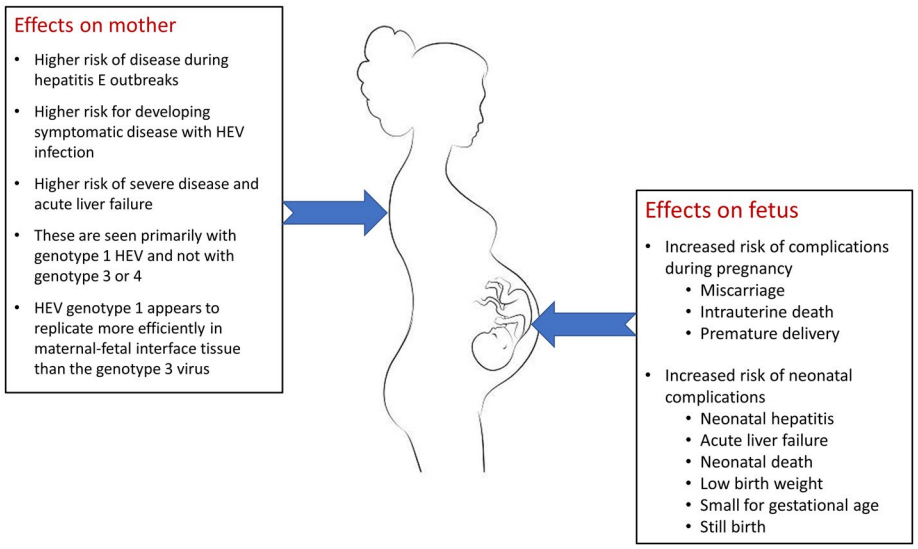

FIG 2 Salient features of HEV infection in pregnant women and their neonates.

and immunological factors have been proposed as being responsible.[10]

In a systematic review of 23 studies, including 18 from India, that examined the outcomes of hepatitis E in pregnant women, maternal mortality rate varied from 3.2% to 70%, with a median of 26%.[11] In a study of 144 pregnant Indian women with HEV infection and acute hepatitis or ALF, HEV RNA was detected in the cord blood in 46% of infants, indicating vertical transmission.[12]

Chronic HEV Infection

HEV viremia persisting for more than 6 months, referred to as chronic hepatitis E, has been recognized in immunosuppressed persons, in particular solid organ transplant recipients and those receiving tacrolimus. Such a chronic infection is caused almost exclusively by GT3 HEV, with occasional cases of GT4 HEV infection. The clinical spectrum of chronic HEV infection is quite broad and ranges from asymptomatic transaminase elevation to acute hepatitis to chronic hepatitis to subacute hepatic failure to ALF to liver cirrhosis. Reduction of immunosuppression leads to resolution in nearly one-third of patients; in those who still do not clear the virus, administration of ribavirin or of pegylated interferon has been found to be effective.

In India, with hepatitis E illnesses caused exclusively by HEV GT1, chronic HEV appears to be rare or nonexistent, even in immunosuppressed persons,[13] with only occasional case reports.[14]

TABLE 2. CONSIDERATIONS FOR THE USE OF HEV VACCINE IN VARIOUS SETTINGS OR POPULATION SUBGROUPS, AS AND WHEN IT BECOMES AVAILABLE IN INDIA

Population Group	Explanations and Comments
General population	• Limited data on safety and efficacy in those aged <16 years or >65 years. • No efficacy data from high-endemic regions such as India where virus inoculum may be larger and hence protective efficacy may be lower. • Vaccine efficacy was proven primarily against genotype 4 HEV, whereas the disease in India is caused by genotype 1.
Pregnant women	• Very limited data on safety of the vaccine during pregnancy. • Effectiveness of vaccine in preventing severe disease is not known.
Patients with preexisting chronic liver disease	• Data on immunogenicity (and safety) in such subjects are lacking. • Limited data on burden of disease or death because of HEV superinfection among patients with chronic liver disease.
Prevention of chronic HEV in immunosuppressed people	• No data on immunogenicity (and safety) in immunosuppressed subjects. • Chronic HEV appears to be infrequent in those with GT1 virus, which is the predominant strain worldwide.
Travelers from low-endemic countries to India	• Current vaccination schedule (0, 1, and 6 months) is too prolonged for use as a travel vaccine.
Prevention and control of HEV outbreaks	• The vaccine schedule (0, 1, and 6 months) is too long to control an outbreak.

Transfusion-Related HEV Transmission

In recent years, HEV has been shown to be capable of transmission through transfusion of contaminated blood or blood products. Such transmission is of particular importance for immunosuppressed transfusion recipients (such as those with prior organ transplantation who are receiving immunosuppressive drugs) because of the risk for the infection becoming chronic and consequent chronic liver damage.

However, the transfusion-transmitted HEV infection has been most often associated with GT3 virus, with only occasional reports of GT4 or GT1[15]; by contrast, as discussed earlier, the most prevalent HEV genotype in India is GT1. Although transmission of HEV through blood transfusion has been reported from India,[16] in a recent study of nearly 1800 Indian blood donors, we could not detect HEV viremia in any.[5] These observations suggest that blood transfusion is unlikely to be a major route of HEV transmission in India. In some European countries, donated blood units are now screened for HEV RNA; this, however, does not appear to be necessary and, in any case, would be difficult to implement in the Indian setting.

HEV Infection as Cause of Decompensated Liver Disease

Only a small proportion of HEV infections are associated with clinical evidence of liver disease. This is believed to be related to a large liver reserve in healthy persons. However, when HEV infection occurs in persons with preexisting chronic liver disease, who have a lower liver reserve, clinical manifestations may be more common, and features of liver decompensation, that is, presentation as acute-on-chronic liver failure, may occur.

In two Indian studies, 44% and 50% of patients with chronic liver disease with recent decompensation had detectable IgM anti-HEV or HEV RNA, respectively, indicating the presence of current HEV infection.[17,18] Furthermore, those with evidence of HEV infection had a higher mortality rate.

HEV VACCINE

The wide geographical distribution and high disease burden associated with HEV have prompted several attempts at developing vaccine candidates against HEV. Of these, two have been tried successfully in humans. One of these has been approved and marketed in China and was recently also approved in Pakistan; it is not yet approved in any other jurisdiction. This vaccine, known as HEV239 (Hecolin), uses a purified 239-amino-acid-long recombinant protein from HEV GT1, produced in *Escherichia coli*.[19] Three intramuscular doses of 30 μg each (at 0, 1, and 6 months) are recommended. In a large phase 3 trial, ~99% of recipients of this vaccine developed an antibody response, which remained detectable for up to 4.5 years. Per-protocol and intention-to-treat analyses showed 100% and 95.5% reduction, respectively, in acute hepatitis E cases among vaccine recipients. Table 2 lists some of the important issues that would need consideration before the vaccine can be rolled out.

This vaccine has not yet undergone any trials in India and is currently not available in India. However, a search of trial registry data show that another recombinant hepatitis E vaccine is undergoing safety evaluation in humans.[20]

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